

Chapter 18. Alzheimer's Disease and Other Dementias

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I. INTRODUCTORY REMARKS

Disease definition, causes, and frequency

The term *dementia* refers to a syndrome characterized by progressive loss of cognitive functions, including memory and language, and changes in personality and behavior. The most common cause of dementia in the elderly is Alzheimer' disease (AD) (about 60%), followed by vascular dementia (VaD) (20%). However, considerable overlap exists between AD and VaD, and these two disorders may be extremes of a spectrum. In particular, the clinical differentiation between these disorders is difficult. AD is characterized by the presence of major impairment in learning and in retaining new information and at least one of the following: impairment of complex tasks, impaired reasoning ability, impaired spatial ability and orientation, and impaired language. In VaD loss of cognitive functions roughly overlaps that of AD, except for the onset or worsening of the symptoms within three months of a stroke and/or presence on neuroimaging of brain infarctions involving cortical or subcortical structures, including white matter. Dementia must be distinguished from *mild cognitive impairment* (MCI), which is a new memory complaint, preferably corroborated by an informant, with objective evidence of impairment of short-term memory, all other cognitive functions being normal, and no substantial interference with daily living activities. MCI is frequently an intermediate stage between normal cognition and dementia and is a risk factor for dementia.

Dementing disorders are followed by an increasing disability resulting in social and occupational decline. Dementia may also occur in younger persons where the etiology includes brain trauma, schizophrenia, multiple sclerosis and AIDS. In underdeveloped countries other infections of the CNS may also be a common cause of cognitive decline.

Over the past two decades, a series of well-conducted epidemiological studies have shown that dementia is a common condition affecting up to 5% of individuals over 65 years in industrialized countries. Most population-based studies indicate a prevalence increasing with age from 1.5/100 between 65 and 69 years to over 30/100 at age 85-89. It is not clear if after age 80-85 the prevalence of the disease is still rising or it tends to stabilize. The incidence of dementia is about 1/100 per year after age 65. In 1997 there were about 2.3 millions individuals with AD in the U.S. (range 1.1 to 4.6 millions) where the number of new cases is about 360,000 each year. Due to the aging of the population, the prevalence of AD in the US will grow about 4-fold within the next 50 years if effective interventions to delay the onset of disease are not developed.

Goals of treatment

There are several goals of the treatment of dementia, including: 1) prevention of disease occurrence; 2) symptomatic improvement; 3) cure of disease; 4) delaying cognitive decline; 5) complete symptomatic control. At present there is no proven treatment that modifies the natural history of the disease or changes its outcome. Potential areas for intervention include: 1) increasing the levels of neurotransmitters involved in cognitive functions; 2) providing neuroprotection to neurons already damaged or showing functional changes; and 3) neuronal regeneration by replacing neurons which have been lost. In the future the goal will be to reverse the natural history of dementia by reversing the typical neuropathological lesions (β -amyloid and tau).

Symptomatic treatment of dementia

The first paper describing an effective symptomatic treatment of dementia was published less than twenty years ago and was a small cross-over study with tacrine, the first cholinesterase inhibitor (ChEI). In the last two decades, several drugs have been tested and approved. Patients with dementia of any severity treated in randomized clinical trials with donepezil, rivastigmine, and galantamine (which represent the main category of ChEI shown to be effective with an acceptable tolerability profile) experience some benefits in cognitive function, activities of daily living and behavior at least during the first year of treatment. Memantine, an NMDA-receptor antagonist, and possibly ginkgo biloba have also been reported to be effective.

Problems with trials on symptomatic treatment of dementia

To the present time, the efficacy of symptomatic drugs is at best modest. However, the results of the published randomized trials must be interpreted in the light of methodological drawbacks, concerning especially the definition and the choice of the appropriate outcome. Many outcome measures have been used in dementia trials. The ideal outcome should be easy to measure and easily collectable at each follow-up over a significant period of time (ideally for several years). These measures should have a good reliability, especially considering that many trials are multicenter-based. Cognitive decline is difficult to measure with the available instruments in a quantitative way. Typical problems are floor and ceiling effects, regression to the mean, learning effects and placebo factors. Moreover the range of changes over a short period is small compared to the possible cognitive range of each scale. More suitable and robust end-points are the following: 1) loss of independence; 2) loss of a specific daily living function; 3) placement in a nursing home. However, these end-points require prolonged follow-up and may be influenced by other environmental factors like the presence of an active caregiver, and economic and social environment.

Cognitive tests include a battery of tests covering memory and other domains including language, constructional abilities, attention/concentration and psychomotor speed. Remote and recent memory must be extensively explored along with recall and recognition for various modalities. Verbal and visuo-spatial memory must be also investigated. The Mini Mental State Examination (MMSE) is generally used as a screening test for cognitive impairment while the Clinical Dementia Rating (CDR) is used for grading disease severity. Although the Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog) fulfils the requirements of a comprehensive cognitive scale, none of the available instruments can be preferred as being more valid and reliable. Although several scales have been proposed to measure the activities of daily living (ADL) and to assess an overall clinical improvement, none has advantages that would justify its preferred use in regulatory trials. Moreover, all these tests have shown acceptable validity and reliability in AD, but not in other dementing disorders. This is of particular concern in some aspects. For example, the MMSE is heavily weighted to memory and left hemisphere functions, e.g. speech.

Criteria for assessing symptomatic improvement

The Aging-Warner consortium established in 1992 that two types of outcomes should be used to assess the efficacy of an anti-dementia product: 1) a global assessment performed by a skilled clinician; 2) a performance-based objective test of cognitive function. The consortium identified the Clinician's Global Impression Scale (CGI) and the Scale ADAS-cog as two preferable instruments. This two-outcome approach has the goal to identify changes that are at the same time clinically meaningful and specific (as determined by cognitive testing) and that are not due to some non-specific effects on the general clinical state. In line with the *Note for Guidance on Medicinal Products* of the European Agency for the Evaluation of Medicinal Products (EMA), the efficacy criteria for a drug tested for the treatment of dementia may include symptomatic improvement (which may be manifest in enhanced cognition, more autonomy and/or improvement in behavioral dysfunction), slowing or arrest of symptom progression, and primary prevention of disease by intervention at a pre-symptomatic stage. The EMA requires a six-month treatment for demonstration of efficacy and one year for maintenance of efficacy. Improvement of symptoms should be assessed in three specific domains: 1) cognition, as measured by neuropsychological tests (cognitive end-point); 2) activities of daily living (functional end-point); and 3) overall clinical response (global end-point). Efficacy variables should be defined for each domain. Primary efficacy variables should include cognitive end-points and the clinical relevance of the improvement in cognition, measured preferably by a functional end-point. The overall benefit should then be measured in terms of the proportion of patients achieving a meaningful benefit (responders). Other end-points include behavioral symptoms, which may be selected as secondary end-points or primary end-points in trials designed to assess control of behavioral abnormalities. The Food and Drug Administration (FDA: <http://www.fda.org>) has similar guidelines with a two-outcome approach to assess the efficacy of a drug (one cognitive and one global assessment measure). The FDA requires three-month duration with at minimum 1000 patients exposed for several weeks in the relevant dosage range.

Prevention of dementia

The methodological concerns with symptomatic treatment trials (e.g., cognitive function testing) also apply to prevention trials. RCTs for prevention require very large sample sizes to ensure enough power to detect a significant reduction in the incidence of dementia. Because of this problem, most of the data available to date are based on observational studies. A possible strong end-point could be the clinical diagnosis of dementia (incidence of disease) in previously non-demented subjects. A clinical diagnosis of MCI has more problems in terms of definition and reliability. An additional problem of prevention trials is the long duration of follow-up necessary. The selection of subgroups at higher risk can make it easier to reach the numbers needed. Higher risk groups could be subjects carrying APO-E4, subjects in older age groups, or subjects with MCI. However, results from studies in such selected groups may not necessarily be generalized to wider populations. The incidence of AD is influenced by several factors, such as age, sex, education, family history of disease and genetic status (APO-e), which may affect the outcome of a trial. In a recent study, Kriyscio and coworkers (1) revised the factors affecting the probability of AD in a preventive trial: length of the follow-up period, accrual, incidence rate of disease, drop-in, drop-out rate and the adherence rate. PREADVISE, which is the largest prevention trial up to date, focuses on assessing the potential protective effect of selenium and vitamin E and plans to enroll 10,700 subjects at 400 sites. Another factor that can increase sample size is the rate of misdiagnosis, especially for mild new cases that could not be identified with the operational diagnostic instruments of the trial.

The use of placebo in dementia trials

Given the great heterogeneity of dementing disorders in terms of symptom profile, overall severity and course, the efficacy of a drug can be demonstrated only by using appropriate controls. The availability of active treatments raises ethical concerns about the use of placebo in patients with dementia. However, use of placebo may still be considered for several reasons: 1) Drug efficacy could possibly be only detected with placebo as a comparator; because superiority against an active control may be difficult to prove. Equivalence or non-inferiority designs (requiring larger samples) may be used as proof of efficacy in studies using active controls, but such studies raise interpretative problems, because the argument could be raised that the reference control was not necessarily efficacious in the population and under the conditions being studied; 2) There is no evidence that available treatments affect the patient's long-term health; 3) The efficacy of cholinesterase inhibitors is at best modest; 4) Lack of effective drugs for the prevention of dementia justifies the use of placebo to test drugs assessed for this indication; 5) There are difficulties in determining rates of adverse effects against active comparators which may also cause adverse effects.

The Quality Standard Subcommittee of the American Academy of Neurology (2) recognized that the use of cholinesterase inhibitors should be considered a standard of care for AD patients, even if the clinical effect is small. This requirement may justify placebo-controlled trials only when the investigational agent is used as add-on to existing treatments.

Issues with informed consent

Putative anti-dementia drugs typically undergo a staggered development process, culminating in double-blind studies, usually with a parallel design in which placebos are employed. Patients asked to participate in controlled trials of an investigational treatment must be informed of any alternative treatment and should be able to explore the positive and negative consequences of the treatments being tested (including the use of placebo) to provide a fully informed consent.

Participation of demented patients in such studies calls for attention to the special circumstances of this population and their needs, including consideration of potential benefits to the patients as well as caregivers, the economic impact, and the expected benefits to the society and science. However, demented patients may not be able to understand the full implications of the study, and may be unduly influenced by researchers and caregivers. In addition, the practice of obtaining proxy consent from the patient's surrogate does not satisfactorily resolve the ethical issues, as the surrogate's decisions usually reflect their

personal rather than the patient's choice. In summary, the inability of patients to fully comprehend the possible implications of the study and the consequent need for the consent to be provided by a surrogate raise notable problems. The investigators and the IRB have an important role in ensuring that drug studies for patients with dementia are performed in a way that provides optimal information and preserves the well-being of patients as well as support for their caregivers.

Biological markers

Biomarkers can be defined as biological compounds that can be measured as indicators of exposure (risk factors of disease), intermediate steps of pathogenic pathways, or different clinical stages of the disease including specific responses to drug therapy. Genetic markers (e.g. the apolipoprotein E genotype) can help to identify subjects who are at higher risk of dementia. Several blood and CSF tests have been proposed for the early detection of AD. Such markers should reflect the pathophysiological mechanisms of AD, an example being the measurement of brain, serum or CSF β -amyloid and tau protein concentrations to detect altered metabolism of amyloid and neurofibrillary degeneration. Tau is a microtubule-associated protein that forms the basic element of the neurofibrillary tangle, one of the characteristic lesions of AD. CSF-tau levels have shown a good sensitivity (85%) and specificity (83%) to distinguish AD patients from normal elderly controls. $A_{\beta 42}$ is a 42 amino acid fragment of the transmembrane amyloid precursor protein (APP) that aggregates as β -pleated sheets in extracellular neuritic plaques. $A_{\beta 42}$ and a shorter 40-amino-acid peptide ($A_{\beta 40}$) can both be assayed in the CSF. Several studies have consistently demonstrated a moderate to marked decrease in CSF $A_{\beta 42}$ in AD, probably because this compound is bound within the neuritic plaques.

At present, no biological marker has been recommended for use in clinical trials of dementia. The use of biological markers could be useful in the future, especially among subjects who are asymptomatic or have MCI, to select subgroups at higher risk to develop dementia. Alternatively, biological markers can be considered as surrogate end-points to assess treatment efficacy. A consensus committee has recently proposed a reclassification of biomarkers for AD in clinical practice (3). These include core markers (those judged to have reasonable evidence for association with key mechanisms of AD pathology) and non-core markers (those felt to be less clearly associated with mechanisms of pathogenesis or neurodegeneration in AD). Core markers include amyloid beta peptide, APP, tau proteins, isoprostanes, A1-antichymotrypsin, interleukin-6-receptor-complex, C-reactive protein, C1q, homocysteine, oxysteroids, 3-nitrotyrosine. Non-core markers include glutamine synthetase, human antibodies against A_{β} -related proteins, glial fibrillary acidic protein, sulfatide, AD7C/NTP, and kallikrein 6.

II. PHASE II STUDIES FOR REGISTRATION OF NEW SYMPTOMATIC DRUGS

II.1. Outline of a typical development plan

During this phase the candidate drug is tested against placebo. The goal of this phase is to document efficacy and to identify the parameters of the treatment regimen (titration, dose regimen, maximal tolerated dose, etc.) most likely to maximize the therapeutic response in patients with well-defined disease. As a rule, phase II studies are designed to maximize efficacy by using the smallest possible number of patients with homogeneous disease characteristics, notably those with fewer concomitant illnesses and less severe impairment, in whom clinical response can be detected over a relatively short time. To increase sensitivity, drug response may also be tested by enrolling patients who responded during a pre-randomization phase. Phase II controlled trials must be preceded by open label exploratory studies to assess titration rates, maximally tolerated doses and pharmacokinetics.

The typical trial design is randomized, placebo-controlled, parallel group testing at least two dose regimens over a short time period. Titration to the predetermined doses should be identified to minimize

drop-outs for adverse effects. Patients included in short term phase II clinical trials should be allowed to participate in long-term trials.

II.2. Short-term phase II studies

II.2.A. Objectives

To evaluate short-term efficacy and tolerability and to detect a correlation between different doses and positive and untoward effects.

II.2.B. Primary end-points

1. Change in cognitive function (measured by psychometric tests)
2. Clinical global impression of change
3. Change in performance of ADL
4. Acceptability of treatment as measured by withdrawal from trial
5. Safety as measured by incidence of adverse events, particularly those leading to withdrawal

II.2.C. Secondary end-points

1. Behavioral disturbances
2. Change in quality of life
3. Effect on caregiver

II.2.D. Exploratory end-points

1. Plasma drug levels
2. Changes in functional imaging
3. Effects on biological markers

II.2.E. Study design

Multicenter, randomized, placebo-controlled, parallel group. A cross-over design may be employed in short-lasting treatment periods and when carry-over effects are insignificant. A screening phase may be used to verify patient eligibility, followed by a prospective baseline period during which cognitive functions are tested and the functional and global clinical activities are measured. After randomization, a titration period is started of sufficient length to achieve steady state conditions. A maintenance period of six months follows under the assumption that during this period there will be a clinically significant progression of the disease (for example, a 4-point change on the ADAS-cog) in the placebo arm. Eligible patients should be free of concomitant illnesses and taking no or few active principles. At the end of the trial, the patient is either withdrawn according to a pre-defined treatment schedule, or he/she enters a long-term phase.

II.2.F. Planned sample

With two treatment arms (active vs placebo), a sample size of about 100 per treatment group is needed with an expected 15% of responders (e.g. a 4-point or greater improvement on the ADAS-cog) in the placebo group, under the assumption to detect a 20% absolute difference in the proportion of responders, with an 80% power, a 5% (two-sided) significance, and a 20% drop-out rate.

II.2.G. Study population

Patients with definite dementia, AD or VaD.

II.2.H. Specific inclusion criteria

- a. Adult female and male patients
- b. MMSE between 10 and 26
- c. Reliable caregiver
- d. Dementia of mild to moderate severity (CDR<3 within 4 weeks prior to entry).

- e. Imaging studies performed during six months prior to entry consistent with the diagnosis.

II.2.I. Specific exclusion criteria

- a. Delirium or impairment of consciousness
- b. Major depression or other significant psychiatric diagnosis
- c. History of drug or alcohol abuse
- d. Other disorders possibly causing dementia
- e. History of hypersensitivity to relevant drugs.
- f. Neoplastic, hepatic, renal or cardiac disorders of significant impact on function or survival
- g. Any disability preventing compliance with test procedures.

II.2.J. Tools for assessing primary end-points

- a. ADAS-cog or other valid and reliable cognitive scale;
- b. CGIC, CIBIC plus or other valid and reliable scale assessing overall clinical impairment

II.2.K. Tools for assessing secondary end-points

- a. PDS, IADL or other valid and reliable scale assessing ADL, quality of life, cognitive and behavioral abnormalities
- b. Caregiver global impression
- c. Nurse global impression

II.2.L. Specific criteria for early withdrawal and discontinuation

- a. Occurrence of significant adverse events thought to impair ADL and overall quality of life
- b. Poor compliance
- c. Withdrawal of consent

II.2.M. Data analysis method

The analysis of treatment efficacy is performed on the intention-to-treat population (all randomized patients receiving at least one dose of study medication). Parametric and non parametric tests are used as appropriate for primary and secondary end-points. Continuous variables (cognitive scores) are tested using parametric tests, like the Student's t test or analysis of variance, and non parametric tests, like the Wilcoxon-Mann Whitney test. Categorical variables (global impression, ADL, IADL, proportion of responders or cases withdrawn from the study, etc.) are tested using the chi-square test (parametric) or the Kruskal-Wallis test (non parametric). Changes in the rate of decline can be assessed with survival analysis (Kaplan-Meier survival curves and Cox's proportional hazard function). Univariate and multivariate statistical techniques can be used as appropriate. All p values should be based on two-sided tests with a 5% significance level.

II.3. Long-term phase II studies

When treatment efficacy is demonstrated in short-term clinical trials, long-term phase II studies are implemented to verify the duration of treatment effects on cognitive, functional and behavioral parameters. The estimated duration of a long-term clinical trial is about 12 months. During this period safety and efficacy are investigated with respect to symptom relief, slowing of progression of cognitive decline, and control of behavioral abnormalities. Ideally, long-term clinical trials are the extension of short-term studies. The dosage of the study medication may be adjusted to achieve the maximally tolerated dose. At study end all patients, including those who were in the placebo arm, should be given the active medication, which should be continued as long as the physician and/or caregiver perceives it to be beneficial, and retention time should be used as a measure of treatment effectiveness and tolerability. Along with cognitive tests, treatment benefits should be measured in terms of effects on hard end-points like time to loss of independence and/or relevant functional impairment.

II.3.A. Objectives

To evaluate long-term efficacy and tolerability of treatment

II.3.B. Primary end-points

- a. Change in cognitive function (measured by psychometric tests)
- b. Clinical global impression of change
- c. Change in performance of ADL
- d. Time to loss of independence and/or relevant functional impairment
- e. Retention time as a measure of treatment efficacy
- f. Acceptability of treatment as measured by withdrawal from trial
- g. Safety as measured by incidence of adverse events leading to withdrawal

II.3.C. Secondary end-points

- a. Behavioral disturbances
- b. Change in quality of life
- c. Effect on caregiver

II.3.D. Exploratory end-points

Effects on biological markers

II.3.E. Study design

Multicenter, randomized, placebo-controlled, parallel group.

II.3.F. Planned sample

Sample size should be calculated on end-points like loss of independence (placement in nursing home) or severe functional impairment; given a 20% expected 12-month rate in the control group, a sample of about 400 per treatment group is needed under the assumption to detect a 10% difference in the proportion of patients achieving the end-point, with a 80% power, a 5% (two-sided) significance, and a 25% drop-out rate.

II.3.G. Study population

As indicated for short-term phase II studies

II.3.H. Specific inclusion criteria

As indicated for short-term phase II studies

II.3.I. Specific exclusion criteria

As indicated for short-term phase II studies

II.3.J. Tools for assessing primary end-points

As indicated for short-term phase II studies

II.3.K. Tools for assessing secondary end-points

As indicated for short-term phase II studies

II.3.L. Specific criteria for early withdrawal and discontinuation

As indicated for short-term phase II studies

II.3.M. Data analysis method

As indicated for short-term phase II studies

III. PHASE III STUDIES FOR REGISTRATION OF NEW SYMPTOMATIC DRUGS

III.1. Outline of a typical development plan

During phase III development at least one large multicenter, randomized, double-blind, placebo-controlled, parallel-group confirmatory trial must be undertaken. A factorial design can also be considered comparing the investigational drug with cholinesterase inhibitors and placebo. Patients to be enrolled should have a definite diagnosis, like probable AD or VaD. In contrast to phase II trials, an effort should be made to include patients representative of those usually seen in clinical practice. As well, the choice of daily drug doses and dose increments should follow the patterns of clinical practice. As with phase II studies, outcome measures must include changes in cognitive scores and functional and behavioral changes. As the goal of phase III studies is to provide evidence of sustained treatment efficacy over a prolonged time period, the estimated length of the study should be about 12 months during which a statistically significant *and* clinically relevant difference should be documented in favor of the experimental treatment. In studies employing a factorial design, an additive effect is also searched in favor of patients receiving the investigational drug and the other active treatment. Having tested the daily dosage with the best therapeutic ratio in phase II trials, in these pivotal studies the drug should be titrated upwards to reach the highest tolerated dose. At the end of the double-blind phase, an open label extension period should also be considered to test the drug over an even longer period of time and under conditions most likely to reproduce the setting of clinical practice.

III.2. Typical phase III study

III.2.A. Objectives

To evaluate sustained efficacy and tolerability in a sample population representative of that seen in clinical practice

III.2.B. Primary end-points

- a. Change in cognitive function (measured by psychometric tests)
- b. Clinical global impression of change
- c. Change in performance of ADL
- d. Time to loss of independence and/or relevant functional impairment
- e. Retention time as a measure of treatment efficacy
- f. Acceptability of treatment as measured by withdrawal from trial
- g. Safety as measured by incidence of adverse events leading to withdrawal

III.2.C. Secondary end-points

- a. Behavioral disturbance
- b. Change in quality of life
- c. Effect on caregiver

III.2.D. Exploratory end-points

Effects on biological markers

III.2.E. Study design

Multicenter, double-blind, placebo-controlled, parallel group with or without factorial design

III.2.F. Planned sample

As with long-term phase II studies.

III.2.G. Study population

Patients with dementia, including probable AD and VaD.

III.2.H. Specific inclusion criteria

- a. Adult female and male patients
- b. MMSE between 10 and 26
- c. Reliable caregiver
- d. Dementia of any severity supported by imaging studies performed during six months prior to entry

III.2.I. Specific exclusion criteria

As indicated for short-term phase II studies

III.2.J. Tools for assessing primary end-points

As indicated for short-term phase II studies

III.2.K. Tools for assessing secondary end-points

As indicated for short-term phase II studies

III.2.L. Specific criteria for early withdrawal and discontinuation

As indicated for short-term phase II studies

III.2.M. Data analysis method

As indicated for short-term phase II studies.

IV. OTHER STUDIES

IV.1. PREVENTION TRIALS IN MILD COGNITIVE IMPAIRMENT (MCI)

IV.1.A. Outline of a developmental plan

As patients with MCI are expected to convert to dementia at a rate of about 10-15% per year, they represent the ideal target for a prevention trial. Using as an end-point the conversion to dementia diagnosed according to the DSM-IV or NINCDS-ADRDA criteria, a three-year trial has sufficient length to document a statistically significant, clinically relevant, and sustained treatment effect. Placebo must be used to detect the effects on disease progression attributable to active treatment. This procedure is however not without problems. MCI patients who convert to AD within 3 years are very likely to have the disease already at baseline, and thus the study is not really designed for prevention of dementia but rather examines the effect of the drug on the rate of cognitive decline. A practical issue is that MCI patients who are recruited do not necessarily develop dementia at the high rate reported in the literature, and may not represent the real world of MCI. In particular, these subjects may have a more benign course because they have a more prolonged course or have higher prevalence of anxiety or depression.

IV.1.B. Representative trial protocol

IV.1.C.i. Objectives

To assess the treatment effects on disease progression and conversion to dementia

IV.1.C.ii. Primary end-point

Time to the diagnosis of dementia.

IV.1.C.iii. Secondary end-points

Time to the diagnosis of AD, VaD, and other dementia types.

IV.1.C.iv. Exploratory end-points

Effects on biological markers.

IV.1.C.v. Study design

Multicenter, double-blind, placebo-controlled, parallel group with or without factorial design.

IV. 1.C.vi. Planned sample

Given the expected 15% 12-month conversion rate on which the treatment response is measured, a sample of about 120 subjects per treatment group is needed under the assumption to detect a 20% in the proportion of responders, with an 80% power, a 5% (two-sided) significance, and a 30% drop-out rate.

IV. 1.C.vii. Study population

Patients with MCI, i.e. individuals with a new deficit in at least one cognitive domain (usually recent memory) but who appear to function independently in ADL.

IV. 1.C.viii. Specific inclusion criteria

- a. Adult female and male patients
- b. Presence of a memory complaint, preferably corroborated by an informant
- c. Objective evidence of impairment of short-term memory (for age)
- d. Otherwise normal cognitive functions
- e. No interference with work, social activities, or other ADL
- f. MMSE > 26 (Absence of dementia)

IV.1.C.ix. Specific exclusion criteria

- a. Major depression, anxiety or other significant psychiatric diagnosis
- b. History of drug or alcohol abuse
- c. Other disorders possibly causing cognitive decline
- d. History of hypersensitivity to relevant drugs
- e. History of (active) neoplasm, hepatic, renal or cardiac disorders, which could affect the patient's survival
- f. Any disability preventing compliance with test procedures

IV.1.C.x. Tools for assessing primary end-points

- a. NINCDS-ADRDA criteria for the diagnosis of probable dementia

IV.1.C.xi. Tools for assessing secondary end-points

- b. DSM-IV criteria for the diagnosis of dementia
- c. NINDS-AIREN criteria for the diagnosis of vascular dementia, Hachinski Ischemic Scale for the assessment of vascular dementia
- d. Work Group on Frontotemporal Dementia and Pick's Disease diagnostic criteria
- e. Consensus Guidelines for the diagnosis of dementia with Lewy bodies

IV.1.C.xii. Specific criteria for early withdrawal and discontinuation

- a. Occurrence of serious adverse events or events thought to impair ADL and quality of life
- b. Poor compliance
- c. Withdrawal of consent.

IV.1.C.xiii. Data analysis method

The analysis of treatment efficacy is performed on the intention-to-treat population. Univariate and multivariate statistical techniques can be used as appropriate (see also short-term phase II studies).

Conversion to dementia (in general and by type) can be assessed with survival analysis (Kaplan-Meier survival curves and Cox's proportional hazard function). All p values are two-sided with a 5% significance level.

IV.2. PREVENTION TRIALS IN ASYMPTOMATIC PATIENTS

IV.2.1. Outline of a developmental plan

A trial on the prevention of dementia in asymptomatic elderly individuals must be designed considering the expected incidence of dementia in the study population and the factors most likely to affect the incidence of the disease. These factors include age, family history of disease, race/ethnicity, education, and genetic background. In addition, the expected number of patients developing dementia depends on the length of the follow-up period and the drop-out rate (mostly caused by death and poor compliance). Several assumptions are thus required for the calculation of the accrual period, the estimate of the sample size, and the duration of the follow-up.

IV.2.2. Representative trial protocol

IV.2.A.i. Objectives

To assess the treatment effects on the incidence of dementia.

IV.2.A.ii. Primary end-point

Reduction of the incidence of dementia.

IV.2.A.iii. Secondary end-points

Reduction in the incidence of dementia in patient subgroups defined by age, education, and genetic factors.

IV.2.A.iv. Exploratory end-points

Effects on biological markers.

IV.2.A.v. Study design

Multicenter, double-blind, placebo-controlled, parallel group with or without factorial design.

IV.2.A.vi. Planned sample

Based on the calculations made for the PREADVISE study, a sample of about 2700 individuals per treatment group is required to halve the incidence of dementia with a 80% power, a 5% level of significance, and a 30% drop-out rate.

IV.2.A.vii. Study population

Asymptomatic elderly individuals.

IV.2.A.viii. Specific inclusion criteria

- a. Female and male patients aged 65 years and older
- b. Normal cognitive functions

IV.2.A.ix. Specific exclusion criteria

- a. Major depression, anxiety or other significant psychiatric diagnosis
- b. History of drug or alcohol abuse
- c. Other disorder possibly causing cognitive decline
- d. History of hypersensitivity to relevant drugs

- e. History of (active) neoplasm, hepatic, renal or cardiac disorders, which could affect the patient's survival
- f. Any disability preventing compliance with test procedures

IV.2.A.x. Tools for assessing primary end-points

NINCDS-ADRDA criteria for the diagnosis of probable dementia

IV.2.A.xi. Tools for assessing secondary end-points

Genetic background can be defined by history taking and APO-E genotype

IV.2.A.xii. Specific criteria for early withdrawal and discontinuation

- a. Occurrence of serious adverse events or events thought to impair ADL and quality of life
- b. Poor compliance
- c. Withdrawal of consent.

IV.2.A.xiii. Data analysis method

The analysis of treatment efficacy is performed on the intention-to-treat population. Univariate and multivariate statistical techniques can be used as appropriate (see also short-term phase II studies). Incidence of dementia (in general and by type) can be assessed with survival analysis (Kaplan-Meier survival curves and Cox's proportional hazard function). All p values are two-sided with a 5% significance level.

IV.3. PRAGMATIC TRIALS

As in other clinical conditions, pragmatic trials are designed to reproduce settings reflecting more closely the use of a drug in clinical practice. Pragmatic trials may be designed to assess the effectiveness of different therapeutic strategies (e.g., early vs delayed treatment) and to test treatment in populations usually not included in regulatory trials (e.g., oldest patients or patients with concurrent disabling disorders). Studies comparing different drugs and allowing dosing flexibility could be considered. Survival analysis with retention time as the primary end-point should be the preferred choice for measuring treatment effectiveness. Other outcome measures could include time to nursing home placement or loss of independence. An intent-to-treat analysis should be performed in all cases. Trial duration may vary according to the type of therapeutic strategy but it should be generally no shorter than 24 months.

IV.4. SPECIAL INDICATIONS

The designs described for phase III clinical trials can also be used for the assessment of efficacy in patients with specific syndromes (dementia associated with cerebrovascular disorders, dementia with Lewy bodies, fronto-temporal dementia). In these cases, the inclusion/exclusion criteria, the primary and secondary end-points, and the relative tools are the same as those used for dementia at large. As with the management of concurrent clinical conditions, the treatment of the underlying disorders (stroke, Parkinsonism, etc.) should be carefully considered in terms of interactions and specific contraindications.

IV.4.i. Studies in Vascular Dementia

Vascular dementia (VaD) is considered the second most common form of dementia after AD worldwide but probably the first in some countries. Cerebrovascular disease can determine VaD with different mechanisms including large-vessel disease with multiple strokes, single strokes in strategic areas, or subcortical lesions with multiple lacunar infarcts and white matter lesions. The diagnosis of VaD is possible when dementia, history of cerebrovascular disease and a relationship between the two disorders is present. The characteristic feature of subcortical VaD is the involvement of executive functions. These include ability to execute complex behaviors and solving-problems ability. MMSE is not a good

instrument to assess executive functions. Several tests (among which the Trail-Making test or the Clock Drawing task) can assess executive functions. These tests should be included in the assessment of the diagnosis and follow-up of VaD.

Several risk factors are associated with cerebrovascular diseases and consequently with VaD.

The prevention of cerebrovascular disease should be the first step in the prevention of VaD. Studies looking at the efficacy of controlling cardiovascular risk factors in the prevention of VaD are few. In the non-demented subjects enrolled in the Syst-Eur study who received antihypertensive treatment the risk of dementia was less than 50% of that of controls (4).

There is growing evidence that in VaD as in AD there is involvement of the cholinergic system. Animal models of stroke-prone spontaneously hypertensive rats present behavior that can be considered similar to memory impairment present in VaD. These rats show reduction of acetylcholine in several areas of the brain including hippocampus. Cholinergic agents have therefore been tested as potential treatments in VaD. In the largest trial, 603 subjects were recruited for a multicenter randomized trial on donepezil in VaD (5). Patients with probable and possible VaD were recruited. Donepezil was found to be effective for patients with VaD using the ADAS-cog and CIBIC –plus as outcome measures.

IV.4.ii. Behavior and mood disturbances in demented subjects

Depression, anxiety, agitation and more serious symptoms like delusions and aggressive behavior are commonly seen in AD. Dementia-related behavioral disturbances have been associated with excess disability, increased caregiver burden, and premature institutionalization. The presence of behavioral disturbances is one of the main reasons for exclusion of patients from clinical trials. Pharmacotherapy is often necessary to treat these disturbances and specific trials are indicated to document efficacy and tolerability for this specific indication. For example, a NIH-sponsored trial is currently recruiting AD patients to study the effects of citalopram and risperidone in people with dementia-related behavior problems.

V. EXAMPLES OF LANDMARK WELL-DESIGNED TRIALS

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